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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SAOUD, CHRISTINE J

ART UNIT	PAPER NUMBER
1647	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/722,495	SPRINGER et al.
Examiner	**Art Unit**
Christine Saoud	1647

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-8, 17-38, and 40* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8, 17-38, and 40* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4

18) ☐ Interview Summary (PTO-413) Paper No(s).

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Claims 1 and 23 have been amended and claims 9-16, 39 and 41-47 have been canceled as requested in the amendment of paper #3, filed 28 November 2000. Claims 1-8, 17-38 and 40 are pending in the instant application.

Priority

2. This application filed under former 37 CFR 1.60 lacks the necessary reference to the prior application because the current status of all nonprovisional parent applications referenced should be included. Correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-8, 17-38 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the substitution of position 89 with either alanine or tyrosine and the substitution of either of positions 101 or 137 with alanine, does not reasonably provide enablement for substitution of those positions with any neutral amino acid or hydrophobic amino acid. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant specification is directed to mutants of human basic fibroblast growth factor wherein the amino acids at positions 89, 101, and/or 137 are substituted with either a neutral or hydrophobic amino acid. The specification defines a neutral amino acid as including serine, threonine, alanine, asparagine, glutamine, cysteine, glycine, and non-naturally occurring analogues thereof. The specification defines a hydrophobic amino acid as tyrosine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, methionine, and non-naturally occurring analogues thereof. The instant specification is broader than the enabling disclosure because alanine is the only amino acid which has been substituted as all three positions and tyrosine has only been substituted at position 89 and one of ordinary skill in the art would not find these substitutions predictive of all the amino acids which are encompassed by the claim limitations of neutral or hydrophobic amino acids. The specification exemplifies the substitution of amino acid positions 89, 101 and 137 with alanine, however, one of ordinary skill in the art would not reasonably conclude that this substitution is predictive and exemplary of the other amino acids which are encompassed by the claims. For example, alanine is a small, neutral amino acid and one would not reasonably conclude that the result obtained with this substitution would be the same as with an amino acid with an acidic side chain, such as aspartate or glutamate, because these are charged amino acids. The substitution of alanine is not predictive of a substitution with cysteine because cysteine is available for disulfide bond formation, and one would expect some odd structural effects from this substitution. Serine and threonine have much larger side chains than alanine, and

the substitution with alanine could not be predictive of these amino acids, which may have steric hindrance issues in the structure of bFGF, and therefore, it is not clear what the biological effect of such a mutation would be. Additionally, tyrosine, phenylalanine, and tryptophan, have large aromatic side chains, so structurally, alanine is not predictive of these amino acids. Methionine is a larger amino acid which has a sulfur-containing side chain, and one of ordinary skill in the art would not find alanine predictive of this amino acid. The claims further encompass leucine, isoleucine, valine, proline, which are either structurally larger (leu, ile, val) or structurally dissimilar (pro) than alanine, therefore, one would not find alanine to be predictive of these amino acid substitution. A proteins function is dependent on its structure, and the size and/or charge and/or chemical nature of the amino acids in that protein can dramatically effect the biological functions of protein. The substitution of alanine at the recited positions in the claims resulted in a bFGF protein that acts as a superagonist, however, one cannot predict from the substitution of alanine at these positions what biological property will be possessed by the other substitutions. This is because alanine is not representative of the other amino acids encompassed by the claims.

The issue here is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. This position is consistent with the decisions in *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) and Amgen Inc. V. Chugai Pharmaceuticals Co. Ltd., 13 USPQ2d, 1737 (1990), and *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988). A review of *In re Wands* clearly points out the factors to be considered in determining whether a disclosure would require undue experimentation and include (1) the

quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. All of these factors are considerations when determining the enablement of an invention.

Further, *In re Wands* determined that the repetition of work which was disclosed in the patent application as producing a composition containing an antibody, which is a naturally occurring compound, did not constitute undue experimentation even if the antibody produced thereby was not identical to those that were disclosed in that application. The instant claims are not limited to naturally occurring compounds and the instant specification does not provide a description of a repeatable process of producing a protein which has the same biological activity as the alanine substitutions. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work described in the instant application, but a substantial inventive contribution on the part of a practitioner which would involve the determination of which substitutions and combinations of substitutions would result in the biological activity of a superagonist. The decisions of *In re Fisher*, Amgen Inc. v. Chugai, and *In re Wands* have been relied upon in the instant rejection and by the court in a recent CAFC decision, Genentech, Inc. V. Novo Nordisk, 42 USPQ2d, 100 (CAFC 1997) because they show that the judicial interpretation of the first paragraph of 35 U.S.C. § 112 requires that the breadth of the claims must be based upon the predictability of the claimed subject matter and not on some standard of trial and error. Unless one has a reasonable expectation that any one material

embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiments which are more likely to work than not without actually making and testing them, then the instant application does not support the breadth of the claims. For this reason, the claims are not commensurate in scope with the enabling disclosure of the instant specification.

5. Applicant refers to a Declaration by Barry Springer. The Declaration under 37 CFR 1.132 filed November 28, 2000 has been considered but is insufficient to overcome the instant rejection of claims because it fails to establish that substitution with either a neutral or hydrophobic amino acid would provide for the biological effect that was seen with a substitution with alanine. In other words, substitution with alanine is not representative of substitution with another amino acid. A protein's function is dependent on its structure, and the size and/or charge and/or chemical nature of the amino acids in that protein can dramatically effect the biological functions of protein. Robson et al. state that "the changing of one amino acid in a sequence gives, by definition, a new protein" and "it cannot be assumed a priori that changing even one amino acid will not significantly, perhaps even drastically, alter the properties of a protein". The substitution of alanine at the recited positions in the claims resulted in a bFGF protein that acts as a superagonist, however, one cannot predict from the substitution of alanine at these positions what biological property will be possessed by the other substitutions. This is because alanine is not representative of the other amino acids encompassed by the claims. For example, cysteine is residue which is included in the list of potential amino acids for substitution, however, it is well known in the art that cysteine is involved with disulfide bonding. It is not predictive that

substitution will result in a biologically active molecule or whether it will provide for unwanted disulfide bonding intermolecularly or intramolecularly. Evidence that not all amino acids with similar amino acid structure can be substituted one for the other can be found in the prior art. For example, substitution of any amino acid for the glycine at position 119 in bovine growth hormone results in a growth hormone antagonist (see Kopchick et al.). Based on the line of reasoning in the instant Declaration, one of ordinary skill in the art would reasonably expect that substitution of the glycine with serine, threonine, alanine, asparagine, glutamine, or cysteine would result in a growth hormone with conserved function. This is clearly not the case. Additionally, much work has been performed with a technique called alanine scanning mutagenesis in which amino acids of the protein are substituted with alanine to find critical residues in protein function. The results of this technique differ in each protein which is tested, however, the prior art clearly demonstrates that substitution of neutral amino acids with alanine does not necessarily preserve protein function (see Cunningham et al., Figure 1). Therefore, one cannot predict based on conservation of amino acid structure or functional group or amino acid classification alone that protein function will be conserved, absent evidence to the contrary.

The Declaration asserts that because position 89 was substituted with tyrosine and generated a super agonist, that positions 101 and 137 could also be substituted with tyrosine and obtain the same effect (see pages 2-3 of the Declaration). This assertion is not persuasive for the reasons provided above because one cannot extrapolate from substitution with alanine at positions 101 and 137 to substitution with tyrosine just because it works at position 89. The biological effect that is seen with alanine is not predictive of what will occur when tyrosine is substituted

there, and substitution at position 89 is not predictive of substitution at positions 101 or 137. This is because protein structure and function is dependent on interaction of amino acids in their primary structure (i.e. amino acid sequence), secondary structure and tertiary structure. Because alanine and tyrosine are very different structurally (tyrosine has an aromatic side chain), they will surely have different interactions with the amino acids which are near them in the three dimensions of the protein, and therefore, one would not necessarily expect the proteins to have the same biological activity, absent evidence to the contrary. The Declaration states that because alanine substitution results in improved mitogenic agonist activity, it is reasonable to expect that when one or more of the 3 positions is replaced with another neutral or hydrophobic amino acid, the improved mitogenic agonist activity of the mutein will also be obtained. However, there is no evidence to support such a conclusion. It is not reasonable to extrapolate to hundreds of different embodiments, or more, based on 6 muteins, only one of which includes a substitution for an amino acid different from alanine. Applicant's disclosure is not commensurate in scope with what is being claimed, nor can one reasonably extrapolate to what is being claimed because the exemplified substitutions are not predictive of the substitutions which are encompassed by the claims for the reasons provided above.

The Declaration urges that the specification teaches how to make and use the claimed invention without undue experimentation because guidance on protein mutagenesis is available and because screening for activity could be performed. This is not persuasive because one of ordinary skill in the art would find substitution of alanine at positions 89, 101 and 137 and substitution of tyrosine at position 89 predictive of substitution of these amino acid positions with

serine, threonine, asparagine, glutamine, cysteine, glycine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, methionine, and non-naturally occurring analogues thereof. Applicant is asserting that because one could make and test for those embodiments which are encompassed by the claims, the claimed mutants are enabled. This is not persuasive nor does it appear to meet the requirements for an enabling disclosure. Experimentation is undue because each embodiment would need to be made and tested because there is not a reasonable expectation that any one embodiment would possess the required activity of the claims. The guidance in the specification is not sufficient to direct the skilled artisan to those embodiments which would more likely than not possess the required activity, the number of embodiments encompassed is quite large, predictability is lacking, there is a lack of guidance in the prior art, and the amount of experimentation is great as every mutant would need to be made and tested for activity. Therefore, experimentation would be undue and the claims are therefore, not enabled by the instant specification, absent evidence to the contrary.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-8, 17-38, and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims encompass the substitution of position 137 with a hydrophobic amino acid, which includes the naturally occurring amino acid of leucine at this position. It is not clear

how the substitution of leucine at position 137 with leucine would provide for a mutein, wherein the specification describes a mutein as having an altered property, structural or functional. Therefore, the claims are indefinite for the recitation of mutein when naturally occurring amino acids are encompassed by the claims.

Claims 1 and 23 recite "comprising the substitution of a neutral and/or hydrophobic amino acid for one or more of the following". This recitation is confusing because it seems to imply that two amino acids could replace one of the recited amino acids. It would appear that the specification only contemplates single amino acid substitution (i.e. a one for one substitution), but the claim encompasses replacement of one amino acid with potentially two amino acids (both neutral and hydrophobic). Clarification appears to be necessary.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-8, 17-38 and 40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,274,712 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims '712 anticipate the pending claims. The claims of the instant application are generic to those of '712, and are therefore anticipated. Furthermore, the embodiments which are claimed in '712 are clearly exemplified in the instant application and clearly encompassed by the instant claims.

Conclusion

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Christine J. Saoud, Ph.D., whose telephone number is (703) 305-7519. The Examiner can normally be reached on Monday to Friday from 7AM to 3PM. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §§ 1.6(d) and 1.8). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternate number. Official papers filed After Final rejection filed by fax should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTINE J. SAOUD
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